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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER
P21632

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
09/926407

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/02726	26 April 2000	28 April 1999

TITLE OF INVENTION

HETEROCYCLIC CARBOXYLIC ACID DERIVATIVES

APPLICANT(S) FOR DO/EO/US

Hiroyuki KAGECHIKA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. _X_ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ___ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. _X_ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. _X_ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. _X_ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. _X_ is attached hereto (required only if not communicated by the International Bureau).
   b. _X_ has been communicated by the International Bureau.
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. _X_ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
7. ___ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ___ are attached hereto (required only if not communicated by the International Bureau).
   b. ___ have been communicated by the International Bureau.
   c. ___ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ___ have not been made and will not be made.
8. ___ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))
9. _X_ An oath or declaration of the inventor(s) (35 U.S.C. .371(c)(4)).
   "Unexecuted"
10. ___ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (U.S.C. 371(c)(5)).

Items 11 to 16 below concern other document(s) or information included:

11. Assignee: INSTITUTE OF MEDICINAL MOLECULAR DESIGN, INC. of Tokyo, JAPAN
12. ___ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ___ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
14. ___ A FIRST preliminary amendment.
    ___ A SECOND or SUBSEQUENT preliminary amendment.
15. ___ A substitute specification.
16. ___ A change of power of attorney and/or address letter.
17. ___ Figure of Drawing to be published_____
18. _X_ Other items or information:
    Cover Sheet and International Application as published in Japanese.
    PCT/RO/101-PCT Request(in Japanese).
    PCT/IPEA/408(in Japanese).
    PCT/IPEA/409.
    PCT/IB/301.
    PCT/IB/304.
    PCT/IB/308.
    PCT/IB/332.
    PCT/IB/338.
    PCT/ISA/210(in English and Japanese).
    Cover Letter under 35 USC 371 and 1.495.
    Claim of Priority.

JC03 Rec'd PCT/PTO 26 OCT 2001

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/926407	INTERNATIONAL APPLICATION NO. PCT/JP00/02726	ATTORNEY'S DOCKET NUMBER P21632

19. ___ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search report has been prepared by the EPO or JPO. . . . . $ 890.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482). . . . . $ 710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO(37 CFR 1.445(a)(2). . . . . $ 740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO. $1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). . . . . $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	RATE		
Total Claims	4 - 20 =	0	X $18.00	$0.00	
Independent Claims	1 - 3 =	0	X $84.00	$0.00	
Multiple dependent claim(s) (if applicable)			+ $280.00	$0.00	
			TOTAL OF ABOVE CALCULATIONS =	$890.00	
___ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$	
			SUBTOTAL =	$890.00	
Processing fee of $130.00 for furnishing the English translation later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					
Extension of Time fee in the amount of $					
			TOTAL NATIONAL FEE =	$890.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +					
			TOTAL FEES ENCLOSED =	$890.00	
				Amount to be refunded	$
				Charged	$

a. X A check in the amount of $890.00 to cover the above fees is enclosed.

b. ___ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0089.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO **CUSTOMER NO. 7055**
AT THE PRESENT ADDRESS OF:
Bruce H. Bernstein
GREENBLUM & BERNSTEIN, P.L.C.
1941 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

007055

PATENT AND TRADEMARK OFFICE

Leslie J. Depperman Reg No

SIGNATURE

Bruce H. Bernstein 33,329

NAME

29,027

REGISTRATION NUMBER

SPECIFICATION

HETEROCYCLIC CARBOXYLIC ACID DERIVATIVES

Technical Field

The present invention relates to substances acting on retinoid receptors that have physiological activities similar to those of retinoids such as retinoic acid or controlling activities on retinoid actions, and medicaments comprising said compounds as active ingredients.

Background Art

Retinoic acid (vitamin A acid), an active metabolite of vitamin A, has extremely important physiological functions inducing differentiation of immature cells under development processes toward mature cells having specific functions, enhancement of cell proliferation and life support action. It has been revealed that various vitamin A derivatives synthesized so far also have similar physiological functions, for example, the benzoic acid derivatives disclosed in Japanese Patent Unexamined Publication (KOKAI) Nos. (Sho)61-22047/1986 and (Sho)61-76440/1986, and the compounds described in Journal of Medicinal Chemistry, 1988, Vol. 31, No. 11, p.2182. "Retinoids" is a general term for retinoic acid and the aforementioned compounds having retinoic acid-like biological activities.

For example, it was proved that all-trans retinoic acid binds as a ligand to the retinoic acid receptor (RAR) present in cellular nucleus, which belongs to the intranuclear receptor super family (Evans, R.M., Science, 240, p.889, 1988), and regulates proliferation and differentiation of animal cells or cellular mortalities (Petkovich, M., et al., Nature, 330, pp.444-450, 1987). It has also been suggested that the aforementioned compounds having the retinoic acid-like biological activities, for example, 4-[(5,6,7,8-tetrahydro- 5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]-benzoic acid: Am80, also bind to RAR in similar manners to retinoic acid to exhibit their physiological actions (see, Hashimoto, Y., Cell Struct. Funct., 16, pp.113-123, 1991; Hashimoto, Y., et al., Biochem. Biophys. Res. Commun., 166, pp.1300-1307, 1990).

Clinically, these compounds were found to be useful for therapeutic and

preventive treatments of vitamin A deficiency disease, hyperkeratosis of epithelial tissue, rheumatism, delayed allergy, bone diseases, leukemia and certain types of cancer. However, due to the variety of biological activities of these retinoids, they are not fully satisfactory medicaments from a viewpoint of side effects. Therefore, it has been desired to create retinoids having characteristic activities and molecules controlling their activities.

As agents for controlling the activities of retinoids, benzodiazepine derivatives such as 4-[5H-2,3-(2,5-dimethyl-2,5 -hexano)-5-methyldibenzo [b,e][1,4]diazepin-11-yl]benzoic acid and 4-[1,3-dihydro-7,8-(2,5-dimethyl -2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl] benzoic acid are known (PCT/JP96/2709, International Publication WO97/11061). Furthermore, diphenylamine type compounds useful as agents for controlling the activities of retinoids are described on International Publication WO98/45242. Although these compounds, per se, have no retinoid action or their retinoid actions are feeble, they have remarkable enhancing actions on retinoids such as retinoic acid. Therefore, they have been suggested to be useful for therapeutic and preventive treatments of vitamin A deficiency disease, hyperkeratosis of epithelial tissue, rheumatism, delayed allergy, bone diseases, leukemia, and certain types of cancer.

As for expression of physiological activities of retinoic acid, existence of retinoid X receptor (RXR, of which ligand is 9-cis-retinoic acid) has been verified. It has been revealed that the retinoid X receptor forms a dimer with the retinoic acid receptor (RAR) to induce or suppress gene transcriptions, thereby controls the expression of the physiological activities of retinoic acid (Mangelsdorf, D.J. et al., Nature, 345, pp.224-229). It has also been revealed that the retinoid X receptor (RXR) binds to the intranuclear receptor of active vitamin D_3, PPAR whose involvement in lipid metabolism is suggested, and other receptors as well as to the retinoic acid receptor (RAR), thereby controls expression of actions of physiologically active substances binding to these receptors, for example, vitamin D_3, thyroxine and the like (Mangelsdorf, D.J. et al., The Retinoids, 2nd Ed., Raven Press, pp.319-350, 1994).

As agents for controlling retinoid actions, compounds are also known to exist which have antagonistic action against retinoids and attenuate typical actions of the above retinoids (Eyrolles, L., et al., Journal of Medicinal Chemistry, 37(10),

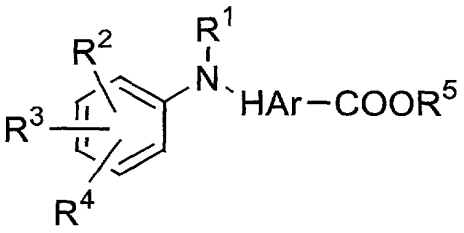
pp.1508-1517, 1994). The above publication discloses that some compounds such as 4-(5H-7,8,9,10-tetrahydro-5,7,7,10,10-pentamethylbenzo[e]naphtho[2,3-b][1,4]-diazepin-13-yl)benzoic acid act as retinoid antagonists. Moreover, certain compounds including 4-(13H-10,11,12,13 -tetrahydro-10,10,13,13,15-pentamethylnaphtho[2,3-b]-[1,2-e][1,4]diazepin-7-yl)benzoic acid have been found as retinoid antagonists by the inventors of the present invention (specification of Japanese Patent Application No. (Hei)7-255912/1995).

Disclosure of the Invention

An object of present invention is to provide substances acting on the retinoid receptor which have retinoid-like bioactivities or bioactivities of controlling the retinoid activities (for example, enhancing or suppressing activities on retinoid). Another object of the present invention is to provide medicaments which comprise said compound as active ingredients. Further object of the present invention is to provide compounds useful as medicaments for preventive or therapeutic treatment of diabetes, and preventive or therapeutic treatment of complications of diabetes such as hyperlipidemia.

The inventors of the present invention conducted various studies to achieve the foregoing objects and found that compounds or salts thereof represented by the following general formula (I) have excellent retinoid-like bioactivities or controlling actions to retinoid bioactivities which are useful as active ingredients of medicaments, for example, those for preventive or therapeutic treatment of diabetes. The present invention was achieved on the basis of the above findings.

The present invention thus provides compounds represented by the following general formula (I):



wherein R^1 represents hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkenyl group, or an

acyl group, R^2 and R^3 independently represent hydrogen atom or a C_{1-6} alkyl group, or adjacent R^2 and R^3 groups may combine together with carbon atoms on the benzene ring to which they bind to form an aromatic 5- to 7-membered ring or non-aromatic 5- to7-membered ring which may be substituted; R^4 represents hydrogen atom, hydroxyl group, a C_{1-6} alkoxyl group, a C_{1-6} alkyl group, nitro group, or a halogen atom; HAr represents a heteroaryl-diyl group consisting of a 5-membered or 6-membered ring which contains 1 to 3 hetero atoms and may be substituted; and R^5 represents hydrogen atom or a C_{1-6} alkyl group.

According to another aspect of the present invention, medicaments comprising a substance, as an active ingredient, which is selected from group consisting of the compounds represented by the aforementioned general formula (I) or physiologically acceptable salts thereof, or hydrates thereof and solvates thereof are provided. These medicaments are useful as agents having retinoid-like actions or agents for controlling retinoid actions (preferably agents for enhancing retinoid activities or suppressing retinoid activities) or useful for preventive and/or therapeutic treatment of diabetes. According to further aspects of the present invention, use of the aforementioned substances for the manufacture of the aforementioned medicaments, and methods for therapeutic and/or preventive treatments of a disease in which a receptor belonging to the intranuclear receptor super family (Evans, R.M., Science, 240, p.889, 1988), preferably a retinoid receptor (RAR and/or RXR) is involved, which comprises the step of administering an effective amount of the aforementioned substances to a mammal including a human are provided.

Best Mode to Carry out the Invention

R^1 represents hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkenyl group, or an acyl group. In the specification, an alkyl group or an alkyl moiety of a functional group having the alkyl moiety (alkoxyl group, for example) may be linear, branched, cyclic or any combination thereof. Examples of the C_{1-6} alkyl group represented by R^1 include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, cyclopropylmethyl group, n-butyl group, sec-butyl group, tert-butyl group, cyclobutyl group, cyclobutylmethyl group, cyclopentyl group, and cyclohexyl group. As the alkyl group represented by R^1, cycloalkyl group or cycloalkylmethyl group is preferred, and cyclopropyl group or cyclopropylmethyl group is more preferred. As the C_{1-6} alkenyl

group represented by R^1, alkenyl group where 1 or 2, preferably 1 double bond is introduced to the aforementioned C_{1-6} alkyl group may be used.

As the acyl group represented by R^1, alkylcarbonyl group, arylcarbonyl group, heterocyclic carbonyl group, arylalkylcarbonyl group, heterocyclic alkylcarbonyl group may be used. In the acyl group exemplified above, monocyclic or fused polycyclic aromatic groups may be used as an aryl moiety. For example, aromatic groups of 1 to 4 ring system, preferably monocyclic or bicyclic aromatic groups may be used. The number of carbon atoms of the aryl group may be 6 to 20, preferably 6 to 16, more preferably 6 to 12, and further preferably 6 to 10. More specifically, examples include phenyl group and naphthyl group.

In the acyl group exemplified above, monocyclic to 4 ring-system heterocyclic groups, preferably monocyclic to 3 ring-system heterocyclic groups, more preferably monocyclic or bicyclic heterocyclic groups, which contain one or more hetero atoms such as nitrogen atom, oxygen atom, and sulfur atom may be used as the hetero ring moiety. When 2 or more hetero atoms are contained, they may be the same or different. The hetero rings may be saturated, partially saturated, or aromatic ring. In the aforementioned acyl group, the hetero ring may bind in any position on the ring. As the hetero ring moiety of the aforementioned acyl group, for example, heteroaryl group such as pyridyl group, or saturated heterocyclic group such as piperazinyl group may be used. However, the hetero rings are not limited to these examples. Example of the acyl group represented by R^1 include, for example, acetyl group, benzoyl group, benzyl carbonyl group, pyridyldimethylcarbonyl group.

The C_{1-6} alkyl group or the acyl group represented by R^1 may be substituted. In the specification, when a functional group is referred to as "may be substituted", the functional group may optionally have one or more arbitrary substituents unless the substituent is not otherwise specified. When a functional group has 2 or more substituents, they may be the same or different. The positions of the substituents are not limited, and substituents may exist in any substitutable positions. The kinds of the substituents are not limited. Examples include, for example, alkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group, halogen atoms (a halogen atom referred to in the specification may be any one of fluorine atom, chlorine atom, bromine atom, or iodine atom), hydroxyl group, oxo group, amino group, ammonium group, imino group, mercapto group, thioxo group, cyano group, nitro group, carboxyl group,

phosphate group, sulfo group, hydrazino group, ureido group, imido group, isothiocyanate group, isocyanate group, alkoxy group, alkylthio group, aryloxy group, hetero cyclic oxy group, arylthio group, hetero cyclic thio group, aralkyl group, hetero cyclic alkyl group, aralkyloxy group, hetero cyclic alkyloxy group, alkoxycarbonyl group, aryloxycarbonyl group, hetero cyclic oxycarbonyl group, alkylcarbonyl group, arylcarbonyl group, hetero cyclic carbonyl group, alkylcarbonyloxy group, arylcarbonyloxy group, hetero cyclic carbonyloxy group, alkylcarbonylamino group, sulfonyl group, sulfinyl group, sulfonylamino group, carbamoyl group, or sulfamoyl.

Furthermore, the substituents exemplified above may be substituted by one or more other substituents. Examples of such groups include hydroxyalkyl group, haloalkyl group, mono or di-alkylamino group, haloalkylcarbonyl group, haloaryl group, hydroxyaryl group, mono or di-alkylcarbamoyl group. However, the above-explained substituents are given solely as examples, and substituents are not limited to these examples.

R^2 and R^3 independently represent hydrogen atom or a C_{1-6} alkyl group. As the C_{1-6} alkyl groups represented by R^2 and R^3, ethyl group or n-propyl group may be preferred, and bulky alkyl group such as isopropyl group, sec-butyl group, isobutyl group, tert-butyl group may also be preferred. When R^2 and R^3 both represent bulky alkyl groups, it is preferable that they substitute at positions on the benzene ring not adjacent to each other. When R^2 and R^3 are adjacent, R^2 and R^3 may combine together with the carbon atom on the phenyl ring to which they bind to form aromatic 5- to 7-membered ring or non-aromatic 5- to 7-membered ring. The ring thus formed may be substituted. Preferably, aromatic 6-membered ring or non-aromatic 6-membered ring may be formed.

For example, R^2 and R^3 may form saturated 5- or 6-membered ring together with 2 carbon atoms on the benzene ring to which each of them binds. The ring thus formed may be substituted with one or more C_{1-4} alkyl group, for example, 2 to 4 methyl groups, preferably 4 methyl groups. For example, it is preferred that the benzene ring substituted with R^2 and R^3 together with R^2 and R^3 forms 5,6,7,8-tetrahydronaphthalene ring and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene ring. An aromatic 6-membered ring may be formed together with 2 carbon atoms on the benzene ring to which each of R^2 and R^3 binds. On the naphthalene ring thus formed, one or more substituents such as a C_{1-6} alkyl group or a

halogen atom may exist.

R^4 represents hydrogen atom, hydroxyl group, a C_{1-6} alkoxyl group, a C_{1-6} alkyl group, nitro group, or a halogen atom. As the C_{1-6} alkoxyl group represented by R^4, for example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, sec-butoxy group, tert-butoxy group, preferably methoxy group may be used. As the C_{1-6} alkyl group represented by R^4, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, isobutyl group or tert-butyl group may be used. As the C_{1-6} alkyl group represented by R^5, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, isobutyl group, or tert-butyl group may be used.

Positions for substitution by R^2 and R^3 are not limited, and R^2 and R^3 may substitute at any position independently. However, when R^2 and R^3 form a ring, it is preferred that each of them is in para position and meta position relative to X, and when R^2 and R^3 do not form a ring, it is preferred that both of them are in meta position relative to X respectively. It is preferred that R^4 is in ortho position relative to X. The position of R^4 is not limited, and R^4 may substitute at any position on the benzene ting.

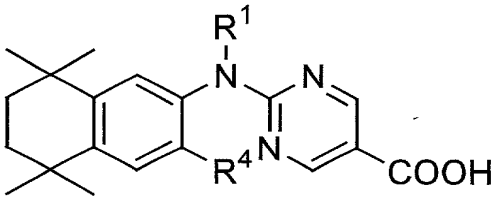
HAr represents a heteroaryl-diyl group consisting of a 5-membered or 6-membered ring which may contain 1 to 3 hetero atoms and may be substituted. The hetero aryl group contains 1 or more, preferably 1 to 3, more preferably 1 or 2 hetero atoms as ring constituent atoms, and may be a monocyclic ring or a fused ring system. When 2 or more hetero atoms are contained, they may be the same or different. As hetero atoms, for example, nitrogen atom, oxygen atom, sulfur atom may be used. Preferably, monocyclic hetero aryl-diyl groups may be used. More specifically, examples include, for example, pyridine-diyl group, pyrazine-diyl group, pyrimidine-diyl group, pyridazine-diyl group, triazine-diyl group, thiophene-diyl group, furan-diyl group, pyrrole-diyl group, imidazole-diyl group, pyrazole-diyl group, thiazole-diyl group, isothiazole-diyl group, oxazole-diyl group, isoxazole-diyl group. However, the heteroaryl-diyl groups are not limited to these examples. Preferably, pyrimidine-diyl group may be used. Positions for bonding of heteroaryl-diyl group are not limited, however, it is preferred that the carboxyl group is in meta or para position relative to X.

The compounds of the present invention may occasionally exist in the form of

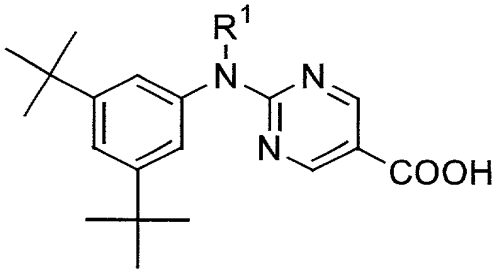
salts such as acid addition salts or base addition salts. Examples of the acid addition salts include mineral acid salts such as hydrochloride or hydrobromide, or organic acid salts such as p-toluene sulfonate, methane sulfonate, oxalate or tartrate. Base addition salts are formed when R^5 represents hydrogen atom. As the base addition salts, metal salts such as sodium salt, potassium salt, magnesium salt or calcium salt, and organic amine salts such as ammonium salt, triethyl amine salt or ethanol amine salt may be used. The compound may also form amino acid salts such as glycine salt.

The compound of the present invention represented by the formula (I) may have one or more asymmetric carbon atoms depending on the kind of substituents. Any optical isomers, any mixtures of optical isomers, and racemate based on these asymmetric carbons, diastereo isomers and any mixtures of diastereo isomers based on 2 or more asymmetric carbons are all encompassed within the scope of the present invention. The compounds which have one or more double bonds may be geometrical isomers in a pure form or mixtures of geometrical isomers. Any hydrates or solvates of the compounds in free form or in the form of a salt also fall within the scope of the present invention.

Preferred examples of the compounds of the present invention represented by the formula (I) are shown below. However, the compounds of the present invention are not limited to these examples.



	R^1	R^4
1	H	H
2	CH_3	H
3	n-C_3H_7	H
4	CH_2-cC_3H_5	H
5	H	CH_3
6	CH_3	CH_3
7	n-C_3H_7	CH_3
8	CH_2-cC_3H_5	CH_3



	R^1
9	CH_3
10	C_2H_5
11	n-C_3H_7
12	CH_2-c-C_3H_5

As for the preparation of the compounds of the aforementioned formula (I), synthetic examples of the aforementioned typical compounds are specifically detailed in the examples given in the specification. Therefore, those skilled in the art will be able to readily prepare any compounds falling within the compounds of the present invention represented by the aforementioned formula (I) by referring to those examples, or if necessary, appropriately altering or modifying the disclosed methods.

The compounds of the aforementioned formula (I) can interact with a retinoid receptor (the term "retinoid receptor" used in the specification encompasses the retinoic acid receptors RAR and RXR, and the term means one or more of receptors with which a retinoid such as all-trans-retinoic acid and 9-cis-retinoic acid can interact), and they, per se, exhibit a retinoid-like physiological activities as an agonist, or have an action for enhancing or suppressing the physiological activities of retinoids. Preferably, they can enhance physiological activities of retinoids.

Therefore, the medicaments comprising the aforementioned compound as an active ingredient are useful as agents having retinoid-like activities or agents for controlling retinoid activities. Which of the actions the compound of the aforementioned formula (I) possesses can be easily determined by a method described in detail in the examples of the specification or methods described the literature. A method for evaluation of compounds enhancing retinoid activities is described in International Publication WO97/11061 (PCT/JP96/2709), and an evaluation for compounds suppressing retinoid activities is described in Eyrolles, L., et al., Journal of Medicinal Chemistry, 37 (10), pp.1508-1517, 1994, and in the specification of Japanese Patent Application No. (Hei)7-255912/1995.

Among the aforementioned compounds, those exhibiting retinoid-like activities have, for example, cell differentiation activity, cell proliferation enhancing activity, life supporting activity, and they can be used as active ingredients of medicaments for preventive or therapeutic treatments of vitamin A deficiency disease, hyperkeratosis of epithelial tissue, psoriasis, allergic diseases, immunological diseases such as rheumatism, bone diseases, leukemia, or cancers. Among the aforementioned compounds, those enhancing retinoid activities, per se, have substantially no retinoid-like activity, or they have slight or moderate retinoid-like activities. However, when those compounds are allowed to coexist with a retinoid such as retinoic

acid, the physiological activities of the retinoid (typical examples include cell differentiation activity, cell proliferation enhancing activity, life supporting activity) are remarkably enhanced.

Although it is not intended to be bound by any specific theory, where the compound enhancing retinoid activities, per se, exhibits retinoid activities, synergistic actions are achieved. Therefore, where retinoids such as retinoic acid or the aforementioned compounds having retinoic acid-like biological activities (for example, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl] benzoic acid: Am80) are administered as medicaments for the preventive or therapeutic treatments of vitamin A deficiency disease, hyperkeratosis of epithelial tissue, psoriasis, allergic diseases, immunological diseases such as rheumatism, bone diseases, leukemia, or cancers, the compounds enhancing retinoid activities can be used as agents that enhance the activities of the retinoids.

Even when retinoids are not administered for the preventive and therapeutic treatments of the aforementioned diseases, the compounds enhancing retinoid activities can increase the activities of retinoic acid that inherently exists in living bodies, and thus the compounds may be administered as medicaments for the purpose of the preventive and therapeutic treatments of the aforementioned diseases. Furthermore, the aforementioned compounds may be used, in addition to the enhancement of the activities of retinoids, to enhance activities of physiologically active substances such as steroid compounds, vitamin D compounds including vitamin D_3, or thyroxine which bind to receptors belonging to the intranuclear receptor super family present in cellular nucleus to exhibit their physiological activities (Evans, R.M., Science, 240, p.889, 1988). They are useful as medicaments for preventive or therapeutic treatments of, for example, diabetes, arteriosclerosis, hyperlipidemia, hypercholesterolemia, bone diseases, rheumatism, immunological diseases.

As the intranuclear receptors, for example, the intranuclear receptor for active vitamin D_3, the PPAR involved in lipid metabolism, the thyroxine receptor, the COUP are known (for these receptors, see, Mangelsdorf, D.J. et al., The Retinoids, 2nd Ed., Raven Press, pp.319-350, 1994). It has been revealed that these receptors bind to the retinoid X receptor (RXR) to have the aforementioned physiologically active substances exhibit their activities.

Among the aforementioned compounds, those suppressing retinoid activities

have an action of markedly suppressing the physiological activities of retinoids (typical examples include cell differentiation activity, cell proliferation enhancing activity, life supporting activity and the like). Although it is not intended to be bound by any specific theory, it is believed that compounds having such an action bind to retinoid X receptor (RXR), which forms a dimer with the retinoic acid receptor (RAR), thereby control the expression of the physiological activity of retinoids such as retinoic acid. These compounds are useful for preventive and/or therapeutic treatments of endogenous hypervitaminosis of vitamin A caused by excessive vitamin A in vivo, or exogenous hypervitaminosis of vitamin A caused by retinoic acid or a compound having retinoic acid-like biological activities (for example, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl] benzoic acid: Am80 or the like) which is administered for therapeutic or preventive treatment of vitamin A deficiency disease, hyperkeratosis of epithelial tissue, psoriasis, allergic diseases, immunological diseases such as rheumatism, bone diseases, leukemia, or cancers.

Cancers such as leukemia can be treated by administering the compounds suppressing retinoid activities, per se, alone or in combination with other retinoid or an antitumor agent. The aforementioned compounds can suppress activities of substances that bind to a receptor belonging to the intranuclear receptor super family present in the nucleus of cells (Evans, R.M., Science, 240, p.889, 1988) to express physiological activities, for example, steroid compounds, vitamin D compounds such as vitamin D_3, thyroxine and orphan receptors whose ligands are unknown. Accordingly, the aforementioned compounds can also be used for controlling the expression of the physiological activities of these substances. The compounds suppressing retinoid activities which bind to the retinoid X receptor (RXR) can be thus used, for example, preventive and/or therapeutic treatments of diseases with abnormalities of biological activities in which one or more of receptors belonging to the intranuclear receptor super family are involved.

According to the most preferred embodiment of the present invention, the medicaments of the present invention may be used for the preventive and/or the therapeutic treatments of diabetes. The cause and morbid state of treatable diabetes are not limited. For example, both of insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) are applicable targets. Those based on the abnormality of insulin reactions (for example, disorders of use of

intracellular glucose, insulin receptor functional disorders, structural abnormality of insulin, those related to administration of glucocorticoid); those based on insulin secretion abnormality (abnormality of signal transmission such as mutation of glucokinase gene, partial destruction of pancrease β cell by pancreatitis and automune mechanism); those by nutrition lesion are all applicable targets of the medicaments of the present invention.

Generally, treatments of diabetes are conducted for the purpose of prevention of the onset of acute and chronic complications or suppression of progression thereof. The medicaments of the present invention may be used for the purpose of preventive and/or therapeutic treatments of the complication of diabetes. The term "preventive treatments" used in the specification should be construed in the broadest sense including the prevention of the onset of diabetes or its complications. Furthermore, the term "therapeutic treatment" used in the specification should be construed in the broadest sense including the fundamental cure of the disease or its complications, remission of symptoms, suppression of progression of morbid state. Examples of the complications of diabetes which are suitable applicable targets of the medicaments of the present invention include, for example, retinopathy, nephrosis, neuropathy, hyperlipidemia. Among them, hyperlipidemia resulting from diabetes is a suitable applicable target of the medicaments of the present invention.

When the medicaments of the present invention are used for the preventive and/or therapeutic treatments of diabetes, or preventive and/or therapeutic treatments of complications of diabetes, they may be used together with other medicaments used for the same purposes. For example, when thiazoline compounds used for the treatment of diabetes or agents having insulin action are used together with the medicaments of the present invention, actions of the medicaments of the present invention may sometimes be enhanced synergistically. Accordingly, combined uses with the above medicaments are preferred embodiments of the medicaments of the present invention. Examples of the thiazoline compounds used for the treatment of diabetes include, for example, troglitazone "Noscal" Sankyo), pioglitazone (disclosed in Japanese Patent Unexamined Publication (KOKAI) No. (Sho) 61-267580/1986), BRL-49652 (disclosed in Japanese Patent Unexamined Publication (KOKAI) No. (Hei) 1-131169 /1989). Examples of the agents having insulin action include insulin, insulin secretion promoting agents (glipemide · Hoechst Marion Roussel Co., Ltd.). In

addition, medicaments such as sulfone urea agents, biguanide-type hypoglycemic agents or α-glucosidase inhibitor may be used in combination.

As the medicament of the present invention, the aforementioned substance, per se, may be administered. However, a pharmaceutical composition for oral administration or parenteral administration may preferably be administered which can be prepared by a method well known to those skilled in the art. Examples of the pharmaceutical compositions suitable for oral administrations include, for example, tablets, capsules, powders, subtilized granules, granules, liquids, and syrups. Examples of the pharmaceutical compositions suitable for parenteral administrations include, for example, injections, suppositories, inhalants, eye drops, nasal drops, ointments, creams, and patches. The aforementioned pharmaceutical compositions may be prepared by the addition of pharmacologically and pharmaceutically acceptable additives. Examples of pharmacologically and pharmaceutically acceptable additives include, for example, excipients, disintegrators and disintegrating aids, binders, lubricants, coating agents, colorants, diluents, base materials, dissolving agents and dissolving aids, isotonic agents, pH modifiers, stabilizers, propellants, and adhesives.

The doses of the medicaments of the present invention are not particularly limited, and appropriate doses are easily selected in various administration methods. For example, for oral administration, the medicament may be used in a dose of 0.01 to 1,000 mg per day for an adult . However, it is desirable that the dose may be suitably increased or decreased depending on the age and body weight of a patient, the presence of complications or symptoms, purpose of treatment or prevention and the like. Also, when medicaments comprising a thiazoline compound or an agent having insulin action as an active ingredient and the medicament of the present invention are used in combination, it is possible to administer the medicament of the present invention during the administration period of the medicaments comprising a thiazoline compound or an agent having insulin action as an active ingredient, and/or in any period before or after said period.

Examples

The present invention will be more specifically explained by examples. However, the scope of the present invention is not limited to the scope of these examples below. Compound numbers in the examples correspond to the compound

numbers of the compounds described as preferred compounds above.

Example 1. Preparation of 2-[N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 1)

A mixture of ethyl 2-chloropyrimidine-5-carboxylate (100 mg), 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-amine (108 mg), and K_2CO_3 (400 mg) was heated at 110°C. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 20 : 1) to give white crystals of ethyl 2-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalen-2-yl)amino]pyrimidine-5-carboxylate (170 mg, 91 %).
Colorless cottons (n-hexane-AcOEt);
^{1}H-NMR (400MHx, $CDCl_3$) δ 8.95 (s, 2 H), 7.56 (br s, 1 H), 7.44 (dd, J = 2.4, 9.0 Hz, 1 H), 7.44 (d, J = 2.4 Hz, 1 H), 7.31 (d, J = 9.2 Hz, 1 H), 4.37 (q, J = 7.0 Hz, 2 H), 1.69 (s, 4 H), 1.39 (t, J = 7.1 Hz, 3 H), 1.30 (s, 6 H), 1.28 (s, 6 H).

Ethyl 2-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)amino]-pyrimidine-5-carboxylate (52 mg) was dissolved in ethanol (3 ml), and the solution was added with a 20% aqueous solution of KOH (0.5 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2N hydrochloric acid, and extracted with Ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 1 (52 mg, quant).
Compound 1:
Colorless prisms (n-hexane-AcOEt); mp >300 °C;
^{1}H-NMR (400MHz, $CDCl_3$) δ 9.94 (s, 1 H), 8.83 (s, 2 H), 7.57 (s, 1 H), 7.55 (d, J = 4.5 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 1 H), 1.65 (s, 4 H), 1.25 (s, 6 H), 1.24 (s, 6 H);
Anal. Calcd for $C_{19}H_{23}N_3O_2 \cdot 1/2H_2O$, C: 68.24 %, H: 7.23 %, N: 12.57 %; Found C: 68.51 %, H: 7.02 %, N: 12.59 %.

Example 2. Preparation of 2-[N-Methyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 2)

Ethyl 2-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)amino]-pyrimidine-5-carboxylate (104 mg) was dissolved in dry DMF (3 ml), and the solution was added with a suspension of NaH (40 mg) in DMF (2 ml). The mixture was then added with methyl iodide (0.5 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 20 : 1) to obtain white crystals of ethyl 2-[N-methyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)amino]pyrimidine -5-carboxylate (105 mg, 97 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 2 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.20 (d, J = 2.2 Hz, 1 H), 7.06 (dd, J = 2.2, 8.2 Hz, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.57 (s, 3 H), 1.70 (s, 4 H), 1.36 (t, J = 7.1 Hz, 3 H), 1.30 (s, 6 H), 1.28 (s, 6 H).

Ethyl 2-[N-methyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)amino]pyrimidine-5-carboxylate (75 mg) was dissolved in ethanol (4 ml), and the solution was added with a 20% aqueous solution of KOH (0.5 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with Ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 2 (70 mg, quant).

Compound 2:

Colorless needles (EtOH); mp >300 °C;

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 2 H), 7.34 (d, J = 8.4 Hz, 1 H), 7.26 (d, J = 2.2 Hz, 1 H), 7.07 (dd, J = 2.2, 8.2 Hz, 1 H), 3.49 (s, 3 H), 1.67 (s, 4 H), 1.27 (s, 6 H), 1.24 (s, 6 H);

Anal. Calcd for $C_{20}H_{25}N_3O_2$, C: 70.77 %, H: 7.42 %, N: 12.38 %; Found C: 70.49 %, H: 7.43 %, N: 12.26 %.

Example 3. Preparation of 2-[N-n-Propyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 3)

Ethyl 2-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)amino]-pyrimidine-5-carboxylate (165 mg) was dissolved in dry DMF (3 ml), and the solution

was added with a suspension of NaH (130 mg) in DMF (2 ml). Then, the mixture was added with n-propyl iodide (0.5 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 20 : 1) to obtain ethyl 2-[N-n-propyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)amino]pyrimidine-5-carboxylate (116.5 mg, 63 %).

Ethyl 2-[N-n-propyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)amino]pyrimidine-5-carboxylate (116.5 mg) was dissolved in ethanol (5 ml), and the solution was added with a 20% aqueous solution of KOH (1 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with Ethyl acetate. The organic layer was dried over Na_2SO_4, and evaporated to give white crude crystals of compound 3 (108 mg, quant).

Compound 3:

Colorless prisms (n-hexane-AcOEt); mp 222 °C;

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.8 (s, 2 H), 7.43 (d, J = 8.5 Hz, 1 H), 7.26 (d, J = 2.3 Hz, 1 H), 7.08 (dd, J = 2.3, 8.5 Hz, 1 H), 3.99 (t, J = 7.8 Hz, 2 H), 1.74 (s, 4 H), 1.66 (6 th, J = 7.1 Hz, 2 H), 1.35 (s, 6 H), 1.31 (s, 6 H), 0.93 (t, J = 7.3 Hz, 3 H);

Anal. Calcd for $C_{22}H_{29}N_3O_2$, C: 71.90%, H: 7.95%, N: 11.44%; Found C: 71.79%, H: 7.99%, N: 11.25%.

Example 4. Preparation of 2-[N-Cyclopropylmethyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 4)

Ethyl 2-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)amino]-pyrimidine-5-carboxylate (100 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (30 mg) in DMF (1.5 ml), and then the mixture was added with cyclopropylmethyl bromide (0.3 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 20 : 1) to obtain ethyl 2-[N-cyclopropyl-

methyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)amino]pyrimidine-5-carboxylate (63 mg, 55 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 2 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.18 (d, J = 2.2 Hz, 1 H), 7.01 (dd, J = 2.2, 8.3 Hz, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 3.86 (d, J = 7.0 Hz, 2 H), 1.70 (s, 4 H), 1.35 (t, J = 7.0 Hz, 3 H), 1.30 (s, 6 H), 1.27 (s, 6 H), 1.17 (br m, 1 H), 0.46 (dd, J = 5.9, 12.6 Hz, 2 H), 0.19 (dd, J = 5.0, 10 Hz, 2 H).

Ethyl 2-[N-cyclopropylmethyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-yl)amino]pyrimidine-5-carboxylate (63 mg) was dissolved in ethanol (4 ml), and the solution was added with a 20 % aqueous solution of KOH (0.5 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 4 (55 mg, 85.5 %).

Compound 4:

Colorless needles (n-hexane-AcOEt); mp 232°C;

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 2 H), 7.36 (d, J = 8.4 Hz, 1 H), 7.22 (d, J = 1.2 Hz, 1 H), 7.02 (dd, J = 1.2, 8.4 Hz, 1 H), 3.84 (d, J = 6.8 Hz, 2 H), 1.67 (s, 4 H), 1.28 (s, 6 H), 1.24 (s, 6 H), 1.18 (br m, 1 H), 0.42 (dd, J = 5.1, 13 Hz, 2 H), 0.14 (dd, J = 5.1, 10 Hz, 2 H);

Anal. Calcd for $C_{23}H_{28}N_3O_2 \cdot 1/10H_2O$, C: 72.64%, H: 7.47%, N: 11.05%; Found C: 72.35%, H: 7.67%, N: 10.81%.

Example 5. Preparation of 2-[N-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 5)

A mixture of ethyl 2-chloropyrimidine-5-carboxylate (424 mg), 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalen-2-amine (497 mg), and K_2CO_3 (1.0 g) was heated at 110°C. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 10 : 1) to give pale yellow crystals of ethyl 2-[N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-naphthalen-2-yl)amino] pyrimidine-5-carboxylate (506 mg, 61 %).

Colorless prisms (n-hexane-AcOEt);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 2 H), 7.69 (s, 1 H), 7.16 (s, 1 H), 4.37 (q, J = 7.1 Hz, 2 H), 2.26 (s, 3 H), 1.69 (s, 4 H), 1.39 (t, J = 7.1 Hz, 3 H), 1.29 (s, 6 H), 1.28 (s, 6 H).

Ethyl 2-[N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-yl)amino]-pyrimidine-5-carboxylate (53 mg) was dissolved in ethanol (2 ml), the solution was added with a 20% aqueous solution of KOH (0.5 ml)and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 5 (49 mg, quant).

Compound 5:

Colorless needles (n-hexane-AcOEt); mp 267 °C;

^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1 H), 8.73 (s, 2 H), 7.20 (s, 1 H), 7.16 (s, 1 H), 2.10 (s, 3 H), 1.64 (s, 4 H), 1.25 (s, 6 H), 1.21 (s, 6 H);

Anal. Calcd for $C_{20}H_{25}N_3O_2$, C: 70.77%, H: 7.42%, N: 12.38%; Found C: 70.49%, H: 7.42%, N: 12.27%.

Example 6. Preparation of 2-[N-Methyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-naphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 6)

Ethyl 2-[N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-yl)amino]-pyrimidine-5-carboxylate (80 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (34 mg) in DMF (1 ml). The mixture was then added with methyl iodide (0.5 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 10 : 1) to obtain white crystals of ethyl 2-[N-methyl-N-5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalen-2-ylamino)pyrimidine-5-carboxylate (80 mg, 96 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1 H), 8.80 (s, 1 H), 7.19 (s, 1 H), 7.05 (s, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 3.47 (s, 3 H), 2.06 (s, 3 H), 1.68 (s, 2 H), 1.68 (s, 2 H), 1.35 (t, J = 7.2 Hz, 3 H), 1.32 (s, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.25 (s, 3 H).

Ethyl 2-[N-methyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalen-2-yl)amino]pyrimidine-5-carboxylate (64 mg) was dissolved in ethanol (3 ml), and the solution was added with a 20 % aqueous solution of KOH (0.5 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 6 (57 mg, 96 %).

Compound 6:

Colorless needles (EtOH); mp >300℃

^{1}H-NMR (400MHz, DMSO-d_6) δ 8.83 (br s, 1 H), 8.68 (br s, 1 H), 7.22 (s, 1 H), 7.14 (s, 1 H), 3.41 (s, 3 H), 1.96 (s, 3 H), 1.65 (s, 4 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.22 (s, 3 H), 1.20 (s, 3 H).;

Anal. Calcd for $C_{21}H_{27}N_3O_2$, C: 71.36%, H: 7.70%, N: 11.89%; Found C: 71.26%, H: 7.74%, N: 11.77%.

Example 7. Preparation of 2-[N-n-Propyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-naphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 7)

Ethyl 2-[N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-yl)amino]-pyrimidine-5-carboxylate (60 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (50 mg) in DMF (2 ml) and stirred. Then, the mixture was added with n-propyl iodide (0.5 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 20 : 1) to obtain a mixture of ethyl 2-[N-n-propyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalen-2-yl)amino]pyrimidine-5-carboxylate and its n-propyl ester derivative (72 mg).

^{1}H-NMR (400 MHz,$CDCl_3$) δ 8.94 (s, 1 H), 8.78 (s, 1 H), 7.18 (s, 1 H), 7.0 (s, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 4.02 (m, 1 H), 3.61 (m, 1 H), 2.05 (s, 3 H), 1.73 (6 th, J = 7.3 Hz, 2 H), 1.69 (s, 4 H), 1.32 (t, J = 7.3 Hz, 3 H), 1.32 (s, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 0.93 (t, J = 7.3 Hz, 3 H).

Ethyl 2-[N-n-propyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalen-2-yl)amino]pyrimidine-5-carboxylate (72 mg) was dissolved in ethanol (3 ml), and the solution was added with a 20 % aqueous solution of KOH (0.5 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 7 (66 mg, quant).

Compound 7:

Colorless needles (n-hexane-AcOEt); mp 193 °C;

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1 H), 8.84 (s, 1 H), 7.21 (s, 1 H), 7.0 (s, 1 H), 4.09 (m, 1 H), 3.64 (m, 1 H), 2.07 (s, 3 H), 1.71 (6 th, J = 7.3 Hz, 2 H), 1.69 (s, 4 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.26 (s, 6 H), 0.95 (t, J = 7.3 Hz, 3 H);

Example 8. Preparation of 2-[N-Cyclopropylmethyl-N-(5,6,7,8-tetrahydro- 3,5,5,8,8-pentamethylnaphthalen-2-yl)amino]pyrimidine-5-carboxylic Acid (Compound 8)

Ethyl 2-[N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-yl)amino]-pyrimidine-5-carboxylate (80 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (45 mg) in DMF (2 ml). The mixture was added with cyclopropylmethyl bromide (0.3 ml) and stirred at 50 °C. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2) to obtain a mixture of ethyl 2-[N-cyclopropylmethyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-yl)amino]pyrimidine-5-carboxylate and its n-cyclopropyl methyl ester (69 mg).

Ethyl 2-[N-cyclopropylmethyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-naphthalen-2-yl)amino]pyrimidine-5-carboxylate (69 mg) was dissolved in ethanol (3 ml), and the solution was added with a 20% aqueous solution of KOH (0.5 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 8 (59 mg, 69 %).

Compound 8:

Pale yellow prisms (CH_3OH); mp 123 °C;

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1 H), 8.83 (s, 1 H), 7.18 (s, 1 H), 7.11 (s, 1 H), 4.10 (dd, J = 6.6, 14.1 Hz, 1 H), 3.47 (d, J = 7.5 Hz, 1 H), 2.08 (s, 3 H), 1.69 (br s, 2 H), 1.68 (br s, 2 H), 1.33 (s, 3 H), 1.27 (s, 3 H), 1.26 (s, 6 H), 1.19 (br m, 1 H), 0.47 (br m, 2 H), 0.22 (br m, 2 H);

Anal. Calcd for $C_{24}H_{31}N_3O_2 \cdot 1/4H_2O$, C: 72.42%, H: 7.98%, N: 10.56%; Found C: 72.45%, H: 7.94%, N: 10.35%.

Example 9. Preparation of 2-[N-(3,5-Di-tert-butylphenyl)-N-methylamino] pyrimidine-5-carboxylic Acid (Compound 9)

A mixture of ethyl 2-chloropyrimidine-5-carboxylate (335 mg), 3,5-di-tert-butylaniline (370 mg), and K_2CO_3 (600 mg) was heated at 110°C. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 10 : 1) to give white crystals of ethyl 2-[N-(3,5-di-tert-butylphenyl)amino]pyrimidine-5-carboxylate (574 mg, 90 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 2 H), 7.47 (d, J = 1.7 Hz, 2 H), 7.41 (s, 1 H), 7.21 (t, J = 1.7 Hz, 1 H), 4.37 (q, J = 7.1 Hz, 2 H), 1.40 (t, J = 7.1 Hz, 3 H), 1.35 (s, 18 H).

Ethyl 2-[N-(3,5-di-tert-butylphenyl)aminopyrimidine-5-carboxylate (50 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (45 mg) in DMF (1 ml). The mixture was then added with methyl iodide (0.3 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 20 : 1) to obtain white crystals of ethyl 2-[N-(3,5-di-tert-butylphenyl)-N-methylamino]-pyrimidine-5-carboxylate (49 mg, 95 %).

^{1}H-NMR ($CDCl_3$) 8.86 (s, 2 H), 7.35 (t, J = 1.8 Hz, 1 H), 7.12 (d, J = 1.8 Hz, 2 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.59 (s, 3 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.34 (s, 18 H).

Ethyl 2-[N-(3,5-di-tert-butylphenyl)-N-methylamino]pyrimidine-5-carboxylate (49 mg) was dissolved in ethanol (4 ml), and the solution was added with a 20 % aqueous solution of KOH (1 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 9 (47 mg, quant).

Compound 9:

Colorless needles (n-hexane-AcOEt); mp 261-263 °C;

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 2 H), 7.31 (br s, 1 H), 7.14 (br s, 2 H), 3.51 (s, 3 H), 1.29 (s, 18 H);

Anal. Calcd for $C_{20}H_{27}N_3O_2 \cdot 1/3H_2O$, C: 69.13%, H: 8.03%, N: 12.10%; Found C: 69.19%, H: 7.78%, N: 11.87%.

Example 10. Preparation of 2-[N-Ethyl-N-(3,5-di-tert-butylphenyl)amino] pyrimidine-5-carboxylic Acid (Compound 10)

Ethyl 2-[N-(3,5-di-tert-butylphenyl)amino]pyrimidine-5-carboxylate (50 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (45 mg) in DMF (1 ml). The mixture was then added with ethyl iodide (0.3 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 10 : 1) to obtain white crystals of ethyl 2-[N-ethyl-N-(3,5-di-tert-butylphenyl)amino]pyrimidine-5-carboxylate (53 mg, 99 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 2 H), 7.37 (t, J = 1.7 Hz, 1 H), 7.06 (d, J = 1.8 Hz, 2 H), 4.33 (q, J = 7.1 Hz, 2 H), 4.05 (q, J = 7.2 Hz, 2 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.34 (s, 18 H), 1.26 (t, J = 7.1 Hz, 3 H).

Ethyl 2-[N-ethyl-N-(3,5-di-tert-butylphenyl)amino]pyrimidine-5-carboxylate (53 mg) was dissolved in ethanol (4 ml), and the solution was added with a 20% aqueous solution of KOH (1 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N

hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 10 (49 mg, 99 %).

Compound 10:

Colorless cottons (n-hexane-AcOEt); mp 277 °C;

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 2 H), 7.34 (br s, 1 H), 7.06 (br s, 2 H), 3.99 (q, J = 7.0 Hz, 2 H), 1.29 (s, 18 H), 1.17 (t, J = 7.0 Hz, 3 H);

Anal. Calcd for $C_{21}H_{29}N_3O_2 \cdot 1/6H_2O$, C: 70.35%, H: 8.25%, N: 11.72%; Found C: 70.37%, H: 8.06%, N: 11.64%.

Example 11. Preparation of 2-[N-(3,5-Di-tert-butylphenyl)-N-n-propylamino]-pyrimidine-5-carboxylic Acid (Compound 11)

Ethyl 2-[N-(3,5-di-tert-butylphenyl)amino]pyrimidine-5-carboxylate (50 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (40 mg) in DMF (1 ml). The mixture was then added with n-propyl iodide (0.3 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 10 : 1) to obtain a mixture of ethyl 2-[N-(3,5-di-tert-butylphenyl)-N-n-propylamino]-pyrimidine-5-carboxylate and its n-propyl ester derivative (56 mg).

Ethyl 2-[N-(3,5-di-tert-butylphenyl)-N-n-propylamino]pyrimidine-5-carboxylate (56 mg) was dissolved in ethanol (4 ml), and the solution was added with a 20% aqueous solution of KOH (1 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give white crude crystals of compound 11 (51.5 mg, 99 %).

Compound 11:

Colorless prisms (n-hexane-CH_2Cl_2); mp 219 °C;

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 2 H), 7.39 (t, J = 1.8 Hz, 1 H), 7.06 (d, J = 1.7 Hz, 2 H), 3.96 (m, 2 H), 1.71 (6th, J = 7.5 Hz, 2 H), 1.34 (s, 18 H), 0.94 (t, J = 7.4 Hz, 3 H);

Anal. Calcd for $C_{22}H_{31}N_3O_2 \cdot 1/5H_2O$, C: 70.82%, H: 8.48%, N: 11.27%; Found C: 70.79%, H: 8.27%, N: 11.18%.

Example 12. Preparation of 2-[N-Cyclopropylmethyl-N-(3,5-di-tert-butylphenyl)-amino]pyrimidine-5-carboxylic Acid (Compound 12)

Ethyl 2-[N-(3,5-di-tert-butylphenyl)amino]pyrimidine-5-carboxylate (50 mg) was dissolved in dry DMF (2 ml), and the solution was added with a suspension of NaH (45 mg) in DMF (1 ml). The mixture was then added with cyclopropylmethyl bromide (0.2 ml) and stirred. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel flash column chromatography (n-hexane : AcOEt = 10 : 1) to obtain a mixture of ethyl 2-[N-cyclopropylmethyl-N-(3,5-di-tert-butylphenyl)amino]-pyrimidine-5-carboxylate and its cyclopropylmethyl ester derivative (55 mg, 96%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 2 H), 7.37 (t, J = 1.7 Hz, 1 H), 7.10 (d, J = 1.7 Hz, 2 H), 4.33 (q, J = 7.1 Hz, 2 H), 3.87 (d, J = 6.8 Hz, 2 H), 1.35 (t, J = 7.2 Hz, 3 H), 1.34 (s, 18 H), 1.26 (br m, 1 H), 0.46 (m, 2 H), 0.18 (d, J = 4.6 Hz, 10.5 Hz, 2 H).

Ethyl 2-[N-cyclopropylmethyl-N-(3,5-di-tert-butylphenyl)amino]pyrimidine-5-carboxylate (55 mg) was dissolved in ethanol (4 ml), and the solution was added with a 20% aqueous solution of KOH (1 ml) and heated at reflux. After the disappearance of the materials was observed with TLC, the reaction mixture was poured into 2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to give compound 12 (51.5 mg, quant).
Compound 12:
Colorless powder (n-hexane-CH_2Cl_2); mp 194 °C;
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 2 H), 7.40 (t, J = 1.8 Hz, 1 H), 7.11 (d, J = 1.8 Hz, 2 H), 3.89 (d, J = 7.0 Hz, 2 H), 1.34 (s, 18 H), 1.18 (br m, 1 H), 0.48 (dd, J = 4.6, 13 Hz, 2 H), 0.20 (dd, J = 5, 10.1 Hz, 2 H);
Anal. Calcd for $C_{23}H_{31}N_3O_2 \cdot 1/3H_2O$, C: 71.28%, H: 8.24%, N: 10.85%; Found C: 71.29%, H: 7.99%, N: 10.73%.

Test Example 1: Cell differentiation-inducing Activity Test in HL-60 Cell

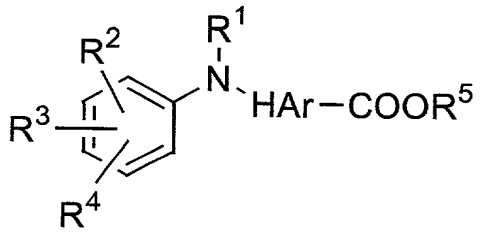
By using the above compounds, cell differentiation-inducing activity of each compound alone, and effect on cell differentiation-inducing action of a co-existing retinoid were examined. As a comparative and co-existing retinoid, Am80: 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid (1×10^{-10} M) was used. According to the method described in Japanese Patent Unexamined Publication (KOKAI) No.(Sho)61-76440/1986, promyelocytic leukemia cell stain HL-60 was used, and differentiation into granulocytic cells was determined by observing morphological change and measuring ability to reduce nitroblue tetrazolium (NBT). The ratios of differentiated cells shown in the following table were calculated from the ability of reducing NBT. The results are shown on Table 1.

Table 1

Ratio of differentiated cells by each compound alone (%)				Ratio of differentiated cells by each compound co-existing with 1×10^{-10} M Am80 (%)					
Compound	Concentration (M)			Concentration (M)					
No.	10^{-8}	10^{-7}	10^{-6}	none	10^{-11}	10^{-10}	10^{-9}	10^{-8}	10^{-7}
1	2	2	44	10	19	17	22	17	39
2	2	37	81	5	6	7	18	81	78
3	9	14	16	11	27	60	90	87	89
4	6	9	6	10	43	71	74	83	89
5	1	3	9	10	18	18	25	49	85
6	2	11	10	5	5	16	58	81	78
7	2	3	2	10	23	53	76	83	82
8	3	4	4	5	9	26	63	84	81
9	2	1	1	2	12	17	14	18	24
10	1	3	2	2	18	15	18	38	81
11	1	2	1	2	18	29	47	87	86
12	2	3	3	2	19	27	59	80	90

What is claimed is:

1. A compound or a salt thereof represented by the following general formula (I):



wherein R^1 represents hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkenyl group, or an acyl group, R^2 and R^3 independently represent hydrogen atom or a C_{1-6} alkyl group or adjacent R^2 and R^3 may combine together with carbon atoms on the benzene ring to which they bind to form an aromatic 5- to 7-membered ring or non-aromatic 5- to 7-membered ring which may be substituted; R^4 represents hydrogen atom, hydroxyl group, a C_{1-6} alkoxyl group, a C_{1-6} alkyl group, nitro group, or a halogen atom; HAr represents a heteroaryl-diyl group consisting of a 5-membered or 6-membered ring which contains 1 to 3 hetero atoms and may be substituted; and R^5 represents hydrogen atom or a C_{1-6} alkyl group.

2. A medicament which comprises the compound according to claim 1 or a physiologically acceptable salt thereof as an active ingredient.

3. The medicament according to claim 2, which is used for preventive and/or therapeutic treatment of diabetes.

4. An agent for controlling retinoid action which comprises the compound according to claim 1 or a physiologically acceptable salt thereof as an active ingredient.

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Declaration and Power of Attorney for Utility or Design Patent Application
特許出願宣言書

Japanese Language Declaration

私は、下欄に氏名を記載した発明者として、以下のとおり宣言する：

私の住所、郵便の宛先および国籍は、下欄に氏名に続いて記載したとおりであり、

名称の発明に関し、請求の範囲に記載した特許を求める主題の本来の、最初にして唯一の発明者である（一人の氏名のみが下欄に記載されている場合）か、もしくは本来の、最初にして共同の発明者である（複数の氏名が下欄に記載されている場合）と信じ、

上記発明の明細書（下記の欄で x 印がついていない場合は、本書に添付）は、

☐ ____年____月____日に提出され、米国出願番号

_____とし、（該当する場合）

____年____月____日に訂正されました。又は、

☐ 特許協定条約国際出願番号_____とし、

（該当する場合）____年____月____日に訂正されました。

私は、前記のとおり補正した請求の範囲を含む前記明細書の内容を検討し、理解したことを陳述する。

私は、連邦規則法典第 37 編第 1 条 56 項に定義されているとおり、特許資格の有無について重要な情報を開示すべき義務があることを認めます。

私は、合衆国法典第 35 部第 119 条（a-d）項又は第 365 条(b)項に基づく、下記の外国特許出願又は発明者証出願、或いは第 365 条(a)項に基づく、少なくても米国以外の 1 カ国を指名した PCT 国際出願の外国優先権を主張し、更に優先権の主張に係わる基礎出願の出願日前の出願日を有する外国特許出願、又は発明者証出願或るいは PCT 国際出願を以下に“なし”の箱に印をつけることにより明記する：

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Heterocyclic Carboxylic Acid Derivatives

the specification of which is attached hereto unless the following box is checked:

☒ was filed on **26/Apr/00** as United States Application Number **09/926,407** and was amended on **26/Oct/01** (if applicable) or,

PCT International Application Number **PCT/JP00/02726** and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority under Title 35, United States Code §119(a-d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States, listed below. I have also identified below, by checking the "No" box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior foreign applications 先の外国出願			Priority claimed 優先権の主張
11-121592 (Number) （番号）	**Japan** (Country) （国名）	**28/Apr/99** (Day/Month/Year Filed) （出願の年月日）	☒ Yes ☐ No あり なし
_____ (Number) （番号）	_____ (Country) （国名）	_____ (Day/Month/Year Filed) （出願の年月日）	☐ Yes ☐ No あり なし

☐ その他の外国特許出願番号は別紙の追補優先権欄にて記載する。

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

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Japanese Language Utility or Design Patent Application Declaration

私は、合衆国法典第 35 部第 119 条(e)項に基づく、下記の合衆国仮特許出願の利益を主張する。

I hereby claim the benefit under Title 35, United States Code §119 (e) of any United States provisional application(s) listed below.

(Application No.) （出願番号）	(Day/Month/Year Filed) （出願の年月日）
(Application No.) （出願番号）	(Day/Month/Year Filed) （出願の年月日）
(Application No.) （出願番号）	(Day/Month/Year Filed) （出願の年月日）

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☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

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I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application No.) （出願番号）	(Day/Month/Year Filed) （出願の年月日）	(Status) （現況） （特許済み、係属中　放棄済み）
(Application No.) （出願番号）	(Day/Month/Year Filed) （出願の年月日）	(Status) （現況） （特許済み、係属中　放棄済み）

☐ その他の合衆国又は国際特許出願番号は別紙の追補優先権欄にて記載する。

☐ Additional U.S. or international application numbers are listed on a supplemental priority sheet attached hereto.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

私、下記署名者は、ここに記載の米国弁護士または代理人に本出願に関し特許商標庁にて取られるいかなる行為に関して、同米国弁護士又は代理人が私に直接連絡なしに私の外国弁護士或るいは法人代表者からの指示を受け取り、それに従うようここに委任する。この指示を出す者が変更の場合には、ここに記載の米国弁護士又は代理人にその旨通知される。

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Docket #: P21632.de1.Doc

Japanese Language Utility or Design Patent Application Declaration

委任状： 私は、下記発明者として、下記に明記された顧客番号を伴う以下の弁護士又は、代理人をここに選任し、本順の手続きを遂行すること並びにこれに関する一切の行為を特許商標庁に対して行うことを委任する。そして全ての通信はこの顧客番号宛に発送される。

顧客番号 7055

現在委任された弁護士は下記の通りである。

Neil F. Greenblum	Reg. No. 28,394
Bruce H. Bernstein	Reg. No. 29,027
James L. Rowland	Reg. No. 32,674
Arnold Turk	Reg. No. 33,094

POWER OF ATTORNEY: As a named inventor, I hereby appoint the attorney(s) and/or agent(s) associated with the Customer Number provided below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

CUSTOMER NUMBER 7055

The appointed attorneys presently include:

Stephen M. Roylance	Reg. No. 31,296
William E. Lyddane	Reg. No. 41,568
William Pieprz	Reg. No. 33,630
Leslie J. Paperner	Reg. No. 33,329

Address: **GREENBLUM & BERNSTEIN, P.L.C.**
1941 Roland Clarke Place
Reston, VA 20191

直接電話連絡先： Direct Telephone Calls to:

GREENBLUM & BERNSTEIN, P.L.C.
(703) 716-1191

唯一のまたは第一の発明者の氏名	Full name of sole or first inventor Hiroyuki KAGECHIKA
同発明者の署名 日付	Inventor's signature Date January 15, 2002
住所	Residence Tokyo, Japan
国籍	Citizenship Japan
郵便の宛先	Post Office Address 2-39-6, Oizumi-machi, Nerima-ku, Tokyo 178-0062, Japan
第二の共同発明者の氏名（該当する場合）	Full name of second joint inventor, if any
同第二共同発明者の署名 日付	Second Inventor's signature Date
住所	Residence
国籍	Citizenship
郵便の宛先	Post Office Address

（第三またはそれ以降の共同発明者に対しても同様な情報および署名を提供すること。）

(Supply similar information and signature for third and subsequent joint inventors.)